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REMARKS/ARGUMENTS

Reconsideration and continued examination of the above-identified application are respectfully requested.

Claims 37-65 are pending in the present application. New claims 37-65 have been added and claims 1-36 are canceled without prejudice or disclaimer. Support for the new claims can be found throughout the present application, including the claims as originally filed. The new claims correspond essentially to claims 1, 4-16, and 18-32 as originally filed, but have been re-numbered and re-grouped as suggested by the Examiner. Claim 37 is a combination of previous claims 1 and 3. Claim 57 is a combination of previous claims 16 and 17. Accordingly, no questions of new matter should arise and entry of this amendment is respectfully requested.

Rejection of the Claims Under 35 U.S.C. §103

At page 2 of the Office Action, the Examiner states that claims 1-32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Powers et al. (U.S. Patent No. 5,543,396) in view of Porter et al. (U.S. Patent No. 5,591,199) and Scharpe et al. (U.S. Patent Application Publication No. 2002/0061839 A1). The Examiner essentially maintains the rejection set forth in the previous Office Action. The Examiner further states that inflammation is the underlying physiological basis of tissue adhesion and suggests that Porter et al. shows that anti-inflammatory agents reduce adhesion formation. This rejection is respectfully traversed.

The present claims are directed, in part, to methods of reducing surgical adhesion formation between tissue surfaces in a vertebrate subject and methods of reducing post-operative adhesion formation in the peritoneum of a warm-blooded mammal. As is generally known in the art, the phrase "adhesion formation" or "tissue adhesion formation" refers to fibrous bands that form

between tissues and organs, often as a result of injury during surgery. As described at the bottom of page 1 and top of page 2 of the present application, adhesion formation and adhesion-free re-epithelialization can result in the build-up of fibrin gel matrix, and if this fibrin deposition is in excess or not removed, the gel matrix serves as a progenitor to adhesions by forming a band or bridge when two tissue surfaces coated with fibrin matrix are apposed. Adhesion formation is a relatively common consequence of surgical procedures, such as, cardiac, thoracic, gynecologic, ophthalmic, and abdominal surgeries (page 3, lines 21-30). Thus, the phrase "surgical adhesion" or "post-operative adhesion," are also used to refer to tissue adhesion formation.

As acknowledged by the Examiner, Powers et al. does not teach or suggest a method of reducing tissue adhesion formation. Contrary to the Examiner's assertion, Porter et al. also does not teach or suggest a method for reducing tissue adhesion formation.

Porter et al. describes providing a stent for supporting a selected region of a body lumen and inhibiting restinosis by preventing "platelet aggregation and adhesion." Porter et al. makes no reference to "tissue adhesion" formation. The term "adhesion" used in Porter et al. refers only to platelet adhesion, a type of cellular adhesion. It is generally known in the art that cellular adhesion refers to the binding of a cell to another cell or another cell matrix and is different from tissue adhesion. In this regard, it should be noted that Porter et al. does not even mention surgical procedures typically associated with tissue adhesion, such as cardiac, thoracic, gynecologic, ophthalmologic, and abdominal surgeries. Providing a stent for supporting a selected region of a body lumen, as discussed in Porter et al., is very different from such surgical procedures. To assist the Examiner, attached are definitions of each term found at the Wikipedia website.

In addition, unlike the present claims, Porter et al. does not teach or suggest the use of inhibitors of a "chymotrypsin-like serine protease." The anti-inflammatory agents described in

Porter et al. (steroids, ibuprofen, aspirin, somatostatin, angiopeptin, and anti-inflammatory peptide 2; cytotoxins, including colchicine, dexamethasone, doxorubicin, methotrexate, and psoralen, antibiotics) are not inhibitors of a "chymotrypsin-like serine protease."

Furthermore, the Examiner's statement that inflammation is the underlying physiological basis of tissue adhesion is not supported by what is generally known in the art. Mast cells may play an important role in the induction of inflammatory responses and studies have shown that adhesion formation in mast-cell deficient mice was significantly less severe than that in normal control mice (see Present Application, page 2). These findings, however, only suggest that mast cells are closely related to adhesion formation. As discussed in the present application, the exact nature of the role of mast cells or which, if any, of the many factors released by mast cells might mediate this role has not been defined. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection of the Claims on the Ground of Non-statutory Provisional Obviousness-type Double Patenting

At page 6 of the Office Action, the Examiner maintains the rejection of claims 1-32 on the ground of non-statutory provisional obviousness-type double patenting as being unpatentable over claims 1-20 of co-pending Application No. 10/544,254 (Miyazaki et al., U.S. Patent Application Publication No. 2006/0122101).

Since this is a provisional rejection, once the remaining rejections described above have been overcome, this provisional rejection should be withdrawn and, if necessary, applied in co-pending U.S. Patent Application No. 10/544,254.

Accordingly, this provisional rejection should be withdrawn once it is the only remaining rejection in the present application.

Renumbering of the Claims

At page 7 of the Office Action, the Examiner also suggests renumbering the claims, so that the claims are properly grouped. The claims have been renumbered, in accordance with the Examiner's suggestions.

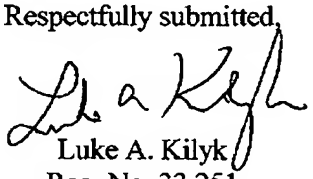
Should the Examiner deem that any further action by Applicants or Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request favorable reconsideration of the present application and a timely allowance of the pending claims.

If there are any fees due in connection with the filing of this response, please charge the fees to Deposit Account No. 50-0925. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such extension is requested and should also be charged to said Deposit Account.

Respectfully submitted,



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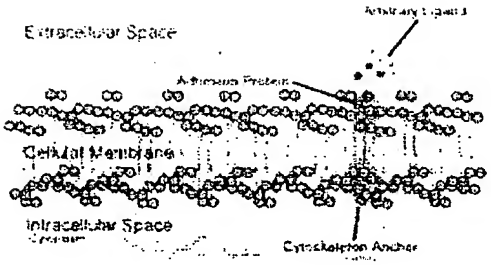
Attachments: "Cell Adhesion" from WIKIPEDIA (3 pages)
"Adhesion (medicine)" from WIKIPEDIA (2 pages)

Cell adhesion

From Wikipedia, the free encyclopedia

Cellular adhesion is the binding of a cell to another cell or to a surface or matrix. Cellular adhesion is regulated by specific cell adhesion molecules that interact with molecules on the opposing cell or surface. Such adhesion molecules are also termed "receptors" and the molecules they recognize are termed "ligands" (and sometimes "counterreceptors").



Schematic of cell adhesion

Since cells are not often found in isolation, rather they tend to stick to other cells or non-cellular components of their environment, a fundamental question is: what makes cells sticky? Cell adhesion generally involves protein molecules at the surface of cells, so the study of cell adhesion involves cell adhesion proteins and the molecules that they bind to.

Contents

Cytoskeletal interactions

For a cell adhesion protein like the one shown in the diagram, the intracellular domain binds to protein components of the cell's cytoskeleton. This allows for very tight adhesion. Without attachment to the cytoskeleton, a cell adhesion protein that is tightly bound to a ligand would be in danger of being hydrolyzed by extracellular hydrolytic enzymes. This will rip out the adhesion protein from the fragile cell membrane. Often the connection between the cell adhesion proteins and the cytoskeleton is not as direct as shown in the diagram. For example, cadherin cell adhesion proteins are typically coupled to the cytoskeleton by way of special linking proteins called "catenins".

Adhesion in Prokaryotes

Prokaryotes have adhesion molecules usually termed "adhesins". Adhesins may occur on pili (fimbriae), flagellae, or the cell surface. Adhesion of bacteria is the first step in colonization and regulates tropism (tissue- or cell-specific interactions).

Adhesion in Viruses

Viruses also have adhesion molecules required for viral binding to host cells. For example, influenza virus has a hemagglutinin on its surface that is required for recognition of the sugar sialic acid on host cell surface molecules. HIV has an adhesion molecule termed gp120 that binds to its ligand CD4, which is expressed on lymphocytes.

Adhesion in Eukaryotes

Eukaryotic protozoans also express multiple adhesion molecules. An example of a pathogenic protozoan is the malarial parasite (*Plasmodium falciparum*), which uses one adhesion molecule called the circumsporozoite protein to bind to liver cells; and another adhesion molecule called the merozoite surface protein to bind red blood cells. In human cells, which have many different types of adhesion molecules, the major classes are named integrins, Ig superfamily members, cadherins, and selectins. Each of these adhesion molecules has a different function and recognizes different ligands. Defects in cell adhesion are usually attributable to defects in expression of adhesion molecules.

Human Genetic Diseases

There are human genetic diseases caused by inability to express a specific adhesion molecule. An example is leukocyte adhesion deficiency-I (LAD-I), where patients do not express the β2-integrin subunit precursor. This integrin is required for leukocytes to adhere to the blood vessel wall during inflammation in order to fight infection. The leukocytes from LAD-I patients fail to adhere and patients exhibit serious episodes of infection that can be life threatening.

Differential Adhesion Hypothesis

The **differential adhesion hypothesis** (sometimes called the "thermodynamic hypothesis") is a theory of **cell adhesion** advanced by Malcolm Steinberg in 1964 to explain the mechanism by which heterotypic cells in mixed aggregates sort out into isotypic territories.[1] The DAH postulates that tissues are viscoelastic liquids, and as such possess measurable tissue surface tensions. These surface tensions have been determined for a variety of tissues, including embryonic tissues and cell lines. The surface tensions correspond to the mutual sorting behavior: the tissue type with the higher surface tension will occupy an internal position relative to a tissue with a lower surface tension (if these tissues can interact with each other through their adhesion machinery). Quantitative differences in homo and heterotypic adhesion are supposed to be sufficient to account for the phenomenon without the need to postulate cell type specific adhesion systems: fairly generally accepted, although some tissue specific cell adhesion molecules are now known to exist.

References

1. ^ http://www.biology-online.org/dictionary/Differential_adhesion

External links

- The Cell (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=cooper.section.2058) by G. Cooper (online textbook)
- Molecular Cell Biology (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=mcb.chapter.6480) by Lodish et al (online textbook)
- Molecular Biology of the Cell (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=adhesion+AND+cell%5Bbook%

5D+AND+cell%5Bbook%5D+AND+cell%5Bbook%5D+AND+8192%5Buid%5D&rid=cell.section.5121) by Alberts et al (online textbook) no anda

- Cell Adhesion and Extracellular Matrix - The Virtual Library of Biochemistry and Cell Biology (http://www.biochemweb.org/adhesion_ecm.shtml)

Retrieved from "http://en.wikipedia.org/wiki/Cell_adhesion"

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Adhesion (medicine)

From Wikipedia, the free encyclopedia

Adhesion (medicine)
Classification & external resources
MedlinePlus 001493 (http://www.nlm.nih.gov/medlineplus/ency/article/001493.htm)

Adhesions are fibrous bands that form between tissues and organs, often as a result of injury during surgery. They may be thought of as internal scar tissue. In the case of frozen shoulder (also known as adhesive capsulitis) adhesions grow between the shoulder joint surfaces, restricting motion.

Adhesions form as a natural part of the body's healing process after surgery. As part of the process, the body deposits fibrin onto injured tissues. The fibrin acts like a glue to seal the injury and encourage deposition of cellular matrix, but may also cause tissues that should be separate to adhere to one another, held together by an adhesion. Over time, as part of the healing process, the body will either breakdown the adhesion and replace it with normal tissue or form a permanent adhesion.

Some adhesions do not cause problems. However, adhesions can prevent tissues and organs from moving freely, sometimes causing organs to become twisted or pulled from their normal positions. Abdominal adhesions are most commonly caused by abdominal surgical procedures, but may also be caused by pelvic inflammatory disease such as endometriosis. The adhesions form within seven days after surgery and may cause internal organs to attach to the surgical site or to other organs in the abdominal cavity. Adhesion-related twisting and pulling of internal organs can result in complications such as infertility and chronic pelvic pain.

Small bowel obstruction (SBO) is another significant consequence of post-surgical adhesions. An SBO may be caused when an adhesion pulls or kinks the small intestine and prevents the flow of content through the digestive tract. Such an event could occur 20 years or more after the initial surgical procedure - if a previously benign adhesion should allow the small bowel to spontaneously twist around itself and obstruct. A SBO is often an emergent condition that could result in death without immediate medical attention. Depending on the severity of the obstruction, a partial obstruction may relieve itself with conservative medical intervention. However, many obstructive events will require re-operation to lyse the offending adhesion(s) or resect the affected small intestine.

As well, adhesions from prior abdominal or pelvic surgery can obscure visibility and access at subsequent abdominal or pelvic surgery. Published reports suggest that a majority of patients that undergo abdominopelvic surgery will be readmitted for surgery within ten years for related or unrelated conditions[1]. Adhesion related complexity at reoperation adds significant risk to subsequent surgical procedures.[2]

Prior to the availability of adhesion barriers, adhesions were documented to be an almost unavoidable consequence of abdominal and pelvic surgery, and occurred in as much as 93% of all patients undergoing abdominal surgery.[3]

External links

- The UK Adhesions Society (http://www.adhesions.org.uk/)
- eMedicineHealth: Adhesions, General and After Surgery

(http://www.emedicinehealth.com/adhesions_general_and_after_surgery/article_em.htm)
- GPnotebook (http://www.gpnotebook.co.uk/simplepage.cfm?ID=1301938201)
- Abdominal Adhesions (http://www.everydayhealth.com/publicsite/index.aspx?puid=3DA46228-905A-47BB-BB1C-A8478D57422B&ContentID=213235&searchTerm=)

References

1. Monk BJ, Berman ML, Montz FJ. Adhesions after extensive gynecologic surgery: clinical significance, etiology, and prevention. Am J Obstet Gynec. 1994;170(5);1396-1403.

2. Van der Krabben AA, Dijkstra FR, Nieuwenhuijzen M, Reijnen MMPJ, Schaapveld M, Van Goor H. Morbidity and mortality of inadvertent enterotomy during adhesiotomy. Br J Surg. 2000;87;467-471.

3. American Society of Reproductive Medicine .
(http://www.cmecorner.com/macmcm/asrm/asrm2002_02.htm)

Categories: Diseases | Diseases involving the fasciae | Abdominal pain